**Seminar 5011 - Desensitization Protocols for Antibiotics and Other Medications**
**Tuesday – 3/22/2011 - 6:45 am to 7:45 am**

**Michael E. Weiss, MD FAAAAI**

## General principles of acute desensitization to medication

In general, desensitization protocols employ the initial administration of low doses (usually, 1:10,000 of a conventional dose)

Oral or parenteral doses are usually doubled every 15 to 30 minutes, and full doses are usually achieved within 4 to 8 hours, although longer intervals are frequently needed for aspirin desensitization

Any remedial risk factor should be corrected. All beta-adrenergic antagonists, including ophthalmic drops, should be discontinued. Asthmatic conditions should be under optimal control.

## Mechanism of acute medication desensitization

The mechanism is a progressive degree of cellular desensitization in mast cells and basophils, induced by a gradual exposure to 'complete' (multivalent) antigen, leading to an increase in the antigen threshold needed for subsequent mediator release

In vitro desensitization of human mast cells deplete syk, an upstream signal transducing molecule necessary for IgE signaling

Naturally occurring syk-deficient basophils are unresponsive to drug antigens, indicating that syk is critical for both activation and desensitization

Morales, Shah & Castells recently showed that IgE mediated desensitization is dependent on STAT 6 (a signal transducer & activator of transcription 6), which is responsible for the transcription of IL-4 and IL-13

Mice, deficient in STAT6 could not be desensitized

## HSR To Chemotherapeutics

There is an ever increasing number of therapeutics used to treat cancer

Despite this large number, hypersensitivity reactions are uncommon except with platinum compounds, taxanes, and L-asparginase

**Platinum compounds-cisplatin and and carboplatin**

Alkylating agents-commonly used for treatment of gynecologic tumors (particularly ovarian) and adenocarcinoma of the lung.

Positive passive transfer in human and monkey and the demonstration of platinum-specific IgE antibody by RAST confirm the type I immunologic nature of sensitivity to platinum compounds in refinery workers.

For patients with platinum-sensitive recurrent cancer, disease relapsing after at least a 6-month disease-free interval, platinum-based chemotherapy remains the most active regimen

**Skin testing - Platinum compounds**

Skin testing may be predictive of increased risk of hypersensitivity reaction

Start with prick puncture test at full strength carboplatin (10 mg/mL)

If prick puncture negative - ID injection of 0.02 mL of 0.1, 1.0, 10 mg/ml (full strength drug) was studied

Skin testing is positive and over 80% of patients with HSR

96% of skin test negative patient's tolerated further courses of medication

Patients with HSR will often have repeat reaction with rechallenge of medication

Pretreatment with steroids and antihistamines do not prevent these reactions

Desensitization can allow these medications to be used

**L-Aspariginase reactions**

L-Aspariginase is an enzyme primarily used to treat ALL

It is derived from E. coli

Administration is associated with a high frequency of hypersensitivity reactions

Skin testing is recommended before the first dose and any time after, if an interval of one week or greater as elapsed between doses

Recommended skin testing is 0.1 mL ID of a 20 IU/ml dilution

This testing is not standardized, reactions have occurred in skin test negative patient's

Options if skin test positive or previous reaction

Switch to the polyethylene glycolated form, PEG- Aspariginase which is better tolerated, especially when given IM

Switch to a form of L-Aspariginase made from Erwinia, a parasitic bacteria (L-Aspariginase made from E. coli is immunologically distinct from preparation from Erwinia)

Desensitization with L-Aspariginase

In some countries there is a shortage of alternative preparations of L-Aspariginase and desensitization may be the only alternative

**Taxanes**

Paclitaxel is used primarily for non-small cell lung, breast and ovarian malignancies

Isolated from the bark of the Pacific yew tree (*Taxus brevifolia*) in the 1970s, and its anti-mitotic activity is due to the bundling of microtubules, which arrests cell division

Docetaxel is a semisynthetic taxane originally extracted from the needles of the European yew tree (*Taxus baccata*)

There is no evidence for IgE antibodies in these HSR's

Reactions typically occur with the first or second dose

Skin test to taxanes in patients with documented HSRs are negative

The mechanism of these reactions is unknown

Slower infusion rates and pre-medication with H1, H2 antihistamine receptor antagonists and steroids decrease the incidence of HSRs

Patients with HSRs to paclitaxel have been switched to docetaxel and this has worked in some, but not all patients

Despite these interventions, some patients with taxane-responsive cancers still present with HSRs to taxanes and may benefit from the reintroduction of the therapy using a desensitization protocol

**Desensitization Protocol**

Pre-medicate - 20 minutes before starting infusion

Singulair 10 mg p.o.
Benedryl 25 mg
Pepcid 20 mg
Aspirin 325 mg

**Monitoring and charting during desensitization**

Document any reaction, including:

Symptoms, vital signs, physical findings

At what step did the reaction occur and how many minutes into the infusion

Treatments administered, response to treatment, when the protocol desensitization was restarted

**Treatment of reactions during desensitization**

For mild reactions:

Isolated itching, flushing, hives, nausea, abdominal pain, back pain with normal vital signs

Stop the infusion and treat with IV Benadryl

Observe the patient until reaction subsides and then resume protocol at the point where the infusion was stopped

For severe reactions:

Hypotension, throat swelling, wheezing/respiratory distress or decreased oxygen saturation

Stop the infusion and treat with epinephrine 0.3 mg IM, Benadryl and Solu-Medrol IV, oxygen, nebulized albuterol for bronchospasm, and IV fluids

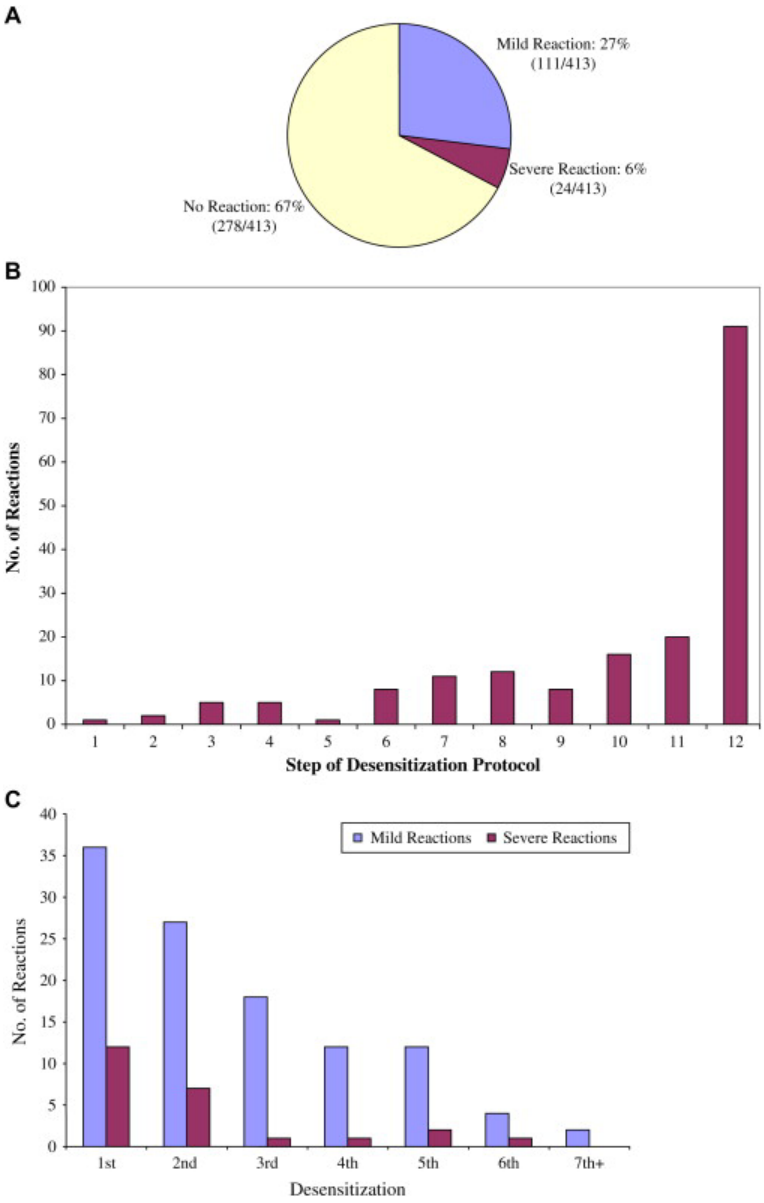
Consider glucagon 1-2 mg bolus IV it patient has taken beta-blockers followed by infusion at 1-5 mg/hour

Immediately alert the housestaff and or allergist on call

When the patient is stable, the protocol will be resumed as instructed by allergist on call

Most reactions occurred during the first desensitization

Reactions were most commonly reported at the last step of the protocol




A, Number and severity of reactions during desensitization. A mild reaction was defined as absence of chest pain, changes in blood pressure, dyspnea, oxygen, desaturation, or throat tightness. A severe reaction included 1 of these.

B, Desensitization step at which reactions occurred (total number of reactions = 180).

C, Desensitization course at which reactions recurred (total number of reactions = 135 [111 mild and 24 severe]).

**Hypersensitivity reactions to mAbs**

HSR to humanized monoclonal antibodies are rare, but there frequency is increasing as patient's are exposed to multiple courses to these agents

The rate of infusion reactions clinically consistent with immediate hypersensitivity is:

5% to 10% for rituximab (Rituxan)
2% to 3% for infliximab (Remicade)
0.6% to 5% for trastuzumab (Herceptin)

(HSRs) have also been reported for omalizumab, natalizumab, basiliximab, abciximab, and cetuximab

Therapeutic mAbs can be divided into 4 subtypes:

fully murine
chimeric (approximately 30% murine) (Rituximab and infliximab)
humanized (approximately 5% murine) (trastuzumab)
fully human

A decrease in antigenicity is expected with a decrease in murine protein sequence, but even a fully human antibody contains nonnative epitopes and can elicit an immunologic

**Desensitization infusion for carboplatin (example)**

| | |
|---|---|
| Target dose (mg) | 549 |
| Standard volume per bag (ml) | 250 |
| Final rate of infusion (ml/hr) | 80 |
| | |
| Calculated target concentration (mg/ml) | 2.196 |
| Standard time of infusion (minutes) | 187.5 |

**3 solutions for carboplatinum desensitization**

| Solution | Volume/ concentration | Total mg Per bag | Amt of bag given (ml) |
|---|---|---|---|
| 1 | 250 ml of 0.022 mg/ml | 5.490 | 9.25 |
| 2 | 250 ml of 0.220 mg/ml | 54.90 | 18.75 |
| 3 | 250 ml of 2.179 mg/ml | 544.679 | 250 |

**12 step Carboplatin desensitization protocol**

| Step | Solution | Rate (ml/hr) | Time (min) | Volume infused | Dose given / step (mg) | Cumulative dose (mg) |
|---|---|---|---|---|---|---|
| 1 | 1 | 2.0 | 15 | 0.50 | 0.0110 | 0.0110 |
| 2 | 1 | 5.0 | 15 | 1.25 | 0.0275 | 0.0384 |
| 3 | 1 | 10.0 | 15 | 2.50 | 0.0549 | 0.0933 |
| 4 | 1 | 20.0 | 15 | 5.00 | 0.1098 | 0.2031 |
| 5 | 2 | 5.0 | 15 | 1.25 | 0.2745 | 0.4776 |
| 6 | 2 | 10.0 | 15 | 2.50 | 0.5490 | 1.0266 |
| 7 | 2 | 20.0 | 15 | 5.00 | 1.0980 | 2.1246 |
| 8 | 2 | 40.0 | 15 | 10.00 | 2.1960 | 4.3206 |
| 9 | 3 | 10.0 | 15 | 2.50 | 5.4468 | 9.7674 |
| 10 | 3 | 20.0 | 15 | 5.00 | 10.8936 | 20.6610 |
| 11 | 3 | 40.0 | 15 | 10.00 | 21.7872 | 42.4482 |
| 12 | 3 | 80.0 | 174.375 | 232.50 | 506.5518 | 549.000 |

Total time (min) = 339.375 = 5.66 hrs

**Desensitization infusion for Paclitaxel (example)**

| | |
|---|---|
| Target dose (mg) | 300 |
| Standard volume per bag (ml) | 250 |
| Final rate of infusion (ml/hr) | 75 |
| | |
| Calculated target concentration (mg/ml) | 1.200 |
| Standard time of infusion (minutes) | 187.5 |

**12 step Paclitaxel desensitization protocol**

| Step | Solution | Rate (ml/hr) | Time (min) | Volume infused | Dose given / step (mg) | Cumulative dose (mg) |
|---|---|---|---|---|---|---|
| 1 | 1 | 2.0 | 15 | 0.50 | 0.006 | 0.006 |
| 2 | 1 | 5.0 | 15 | 1.25 | 0.015 | 0.021 |
| 3 | 1 | 10.0 | 15 | 2.50 | 0.030 | 0.051 |
| 4 | 1 | 20.0 | 15 | 5.00 | 0.060 | 0.111 |
| 5 | 2 | 5.0 | 15 | 1.25 | 0.150 | 0.261 |
| 6 | 2 | 10.0 | 15 | 2.50 | 0.300 | 0.561 |
| 7 | 2 | 20.0 | 15 | 5.00 | 0.600 | 1.161 |
| 8 | 2 | 40.0 | 15 | 10.00 | 1.200 | 2.361 |
| 9 | 3 | 10.0 | 15 | 2.50 | 3.000 | 5.361 |
| 10 | 3 | 20.0 | 15 | 5.00 | 6.000 | 11.361 |
| 11 | 3 | 40.0 | 15 | 10.00 | 12.000 | 23.351 |
| 12 | 3 | 80.0 | 184.4 | 232.50 | 276.639 | 300.000 |

Total time (min) = 348 = 5.8 hrs